

### REMARKS

Claims 1, 3-27 and 29-46 are pending. Applicants elect with traverse Group X (claims 6-15, 33 and 42-46 as related to SEQ ID No. 5 encoding the CobS protein) for examination on the merits. Although not included in Group X, claims 29-31 and 40-41 should also be included in the elected invention because they contain the limitations of claim 10. Applicants reserve the right to prosecute nonelected subject matter in a further patent application.

The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. Support for amended claim 6 may be found, inter alia, at page 15, line 27, to page 16, line 1, and the table (C: SEQ ID NOS:5 and 6) at page 14 of the specification and original claims 1 to 3. Support for amended claim 7 may be found, inter alia, at page 7, line 22, to page 8, line 1, and page 9, lines 20-26, of the specification. Support for new claim 41 is similar to amended claim 6 except for page 5, lines 11-14, and the table (B: SEQ ID NOS:3 and 4) at page 14 of the specification. Support for new claim 42 may be found, inter alia, at page 21, lines 17-24, page 57-60 (Examples 8 and 9), and the table (Examples 8 and 9) at page 60 of the specification; original claim 10; and amended claim 41. Support for new claims 43 to 45 may be found, inter alia, in original claim 12 and new claim 41, original claim 14 and new claim 42, and original claim 15 and new claim 44 respectively.

Notwithstanding the above election, reconsideration of the restriction requirement is requested because examination of all pending claims would not constitute a serious burden. Although the inventions identified by the Examiner are separately patentable, both the need for compact prosecution and the public interest would be served by examination of all claims in a single application. Therefore, claims 1, 3-5, 16-27, 29-32 and 34-41 should not be withdrawn from consideration in this application.

In the alternative, Applicants disagree with the allegation in the Action that claim 6 and those claims depending therefrom lack unity of invention, and therefore belong to different groups of inventions. Although they agree with the Examiner's conclusion that the inventions are separately patentable, Applicants' traversal is based on the pending claims being so linked as to form a single general inventive concept under PCT Rule

13.1. In particular, Groups IX to XII share a special technical feature. These groups relate directly or indirectly to polynucleotides encoding for the CobS protein, taken alone or in combination with the CobU protein. As mentioned above with respect to CobS, alone or in combination with CobU, the cited prior art document does not disclose this special technical feature. Therefore, claims 1, 3-5, 16, 23-24, 27 and 37 should not be withdrawn from consideration in this application.

Group X relates to a polynucleotide coding for a CobS protein which is derived from *Propionibacterium freudenreichii* or a derivative thereof, a vector comprising the polynucleotide, a host cell modified with the polypeptides, and to a process to produce the polypeptide or vitamin B<sub>12</sub> using the modified host cells. More specifically, it also relates to polynucleotides which together with the polynucleotide encoding for the CobS protein or a derivative thereof also comprise a polynucleotide coding for a CobU protein which is derived from *Propionibacterium freudenreichii* or a derivative thereof. The new claims relate to the corresponding polynucleotide and vector comprising both genes and optionally a gene coding for a CobA protein, corresponding modified host cells and to a process to produce the polypeptide or vitamin B<sub>12</sub> using the modified host cells.

The CobS and CobU enzymes are involved in the same step (i.e., the final step) of vitamin B<sub>12</sub> synthesis. This final step is the conversion of the precursor compound II (adenosylcobinamide) into the end product with structure IIC (adenosylcobalamin) (see pages 37-38 and 40-43 of the specification). This conversion is done in three distinct reaction steps via intermediates IIA and IIB. The enzyme CobU catalyzes the first two of these reaction steps and the enzyme CobS the third reaction step.

The cited Roessner *et al* document neither teaches nor suggests the CobS or CobU proteins nor the genes encoding them which are derived from *Propionibacterium freudenreichii*. As indicated at page 1848, second column, last paragraph, Roessner *et al* identifies 16 genes derived from *Propionibacterium freudenreichii* that are responsible for the transformation of uroporphyrinogen III into adenosylcobinamide. In contrast, the CobS and CobU enzymes are responsible for the final step of vitamin B<sub>12</sub> biosynthesis: i.e., the conversion of adenosylcobinamide into vitamin B<sub>12</sub> as described in more detail above. Although the names CobU and CobS appear in Table 1 on page 1846, they only

relate to genes derived from *Salmonella typhimurium*. Since in this bacterium the synthesis of vitamin B<sub>12</sub> occurs through an anaerobic pathway, such as in *P. freudenreichii*, the nomenclature of *S. typhimurium*, including the naming of genes such as CobU and CobS, is also used for *P. freudenreichii*. But the genes from *P. freudenreichii* were not disclosed in Roessner et al. They were disclosed for the first time by Applicants.

Applicants surprisingly found that the overexpression of the genes coding for the CobU and CobS protein, which are involved in catalyzing the final conversion in the vitamin B<sub>12</sub> biosynthetic pathway, results in an increase in vitamin B<sub>12</sub> production (see Example 8). This surprising result is neither taught nor suggested in the above-cited prior art. A combination of the overexpression of the CobU and CobS proteins with the overexpression of the CobA protein surprisingly produces an even further increase in vitamin B<sub>12</sub> production level (see Example 9).


Furthermore, under the Commissioner's Notice of March 26, 1996 (1184 OG 86) implementing the Federal Circuit's decisions of *In re Ochiai*, 37 USPQ2d 1127 (1995) and *In re Brouwer*, 37 USPQ2d 1663 (1996), Applicants request rejoinder of nonelected method claims upon an indication that an elected product claim is allowable.

Applicants earnestly solicit an early and favorable examination on the merits. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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